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### CREATING MARKETS FOR NEW VACCINES PART II: DESIGN ISSUES

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Creating Markets for New Vaccines  
Part II: Design Issues  
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### **ABSTRACT**

Several programs have been proposed to improve incentives for research on vaccines for malaria, tuberculosis, and HIV, and to help increase accessibility of vaccines once they are developed. The U.S. administration's budget proposes a tax credit that would match each dollar of vaccine sales with a dollar of tax credit. The World Bank has proposed a \$1 billion fund to provide concessional loans to countries to purchase vaccines if and when they are developed. European political leaders have spoken favorably about the concept of a vaccine purchase fund. This paper explores the design of such programs, focusing on commitments to purchase new vaccines.

For vaccine purchase commitments to spur research, potential vaccine developers must believe that the sponsor will not renege on the commitment once vaccines have been developed and research costs sunk. Courts have ruled that similar commitments are legally binding contracts. Given appropriate legal language, the key determinant of credibility will therefore be eligibility and pricing rules, rather than whether funds are physically set aside in separate accounts. The credibility of purchase commitments can be enhanced by specifying rules governing eligibility and pricing of vaccines in advance and insulating those interpreting these rules from political pressure through long terms.

Requiring candidate vaccines to meet basic technical requirements, normally including approval by some regulatory agency, such as the U.S. FDA, would help ensure that funds were spent only on effective vaccines. Requiring developing to contribute co-payments would help ensure that they felt that the vaccines were useful given the conditions in their countries.

The U.S. Orphan Drug Act's success in stimulating research and development is widely attributed to a provision awarding market exclusivity to the developer of the first drug for a condition unless subsequent drugs are clinically superior. Purchases under a vaccine purchase program could be governed by a similar market exclusivity provision.

A purchase commitment program could start by offering a fairly modest price. If this proved inadequate to spur sufficient research, the promised price could be increased. This procedure mimics auctions, which are often efficient procurement methods when costs are unknown. As long as prices do not rise at a rate substantially greater than the interest rate, vaccine developers would not have incentives to withhold vaccines from the market.

The World Bank has termed health interventions costing less than \$100 per year of life saved as highly cost effective for poor countries. If donors pledge approximately \$250 million per year for each vaccine for ten years, vaccine purchases would cost approximately \$10 per year of life saved. It is unlikely that vaccines for all three diseases would be developed simultaneously, but if donors wanted to limit their exposure, they could cap their total promised vaccine spending under the program, for example at \$520 million annually. No funds would be spent or pledges called unless a vaccine were developed.

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Several initiatives have recently been proposed to create incentives for research on vaccines against diseases such as malaria, tuberculosis, and AIDS, and to increase accessibility of vaccines once they are developed. The president of the World Bank recently said that the institution is planning to establish a \$1 billion fund to help finance purchases of new vaccines, if and when they are developed [Financial Times, 2000]. The U.S. administration's 2000 budget includes a tax credit for vaccine sales that would effectively double the developing country market for new vaccines against diseases that kill more than one million people each year [<http://www.treas.gov/taxpolicy/library/grnbk00.pdf>]. The tax credits would be capped at \$1 billion over ten years. The concept of a vaccine purchase fund has also received support from European political leaders [[www.auswartiges.amt.de](http://www.auswartiges.amt.de), 1999].

Although malaria, tuberculosis, and African strains of AIDS kill almost 5 million people each year, they are the subject of little vaccine research. Potential vaccine developers fear that they would not be able to sell enough vaccines at a high enough price to recoup their research investments. This is both because these diseases primarily affect poor countries, and because vaccine markets are severely distorted. The proposed programs could both create incentives for vaccine research and help improve access to any vaccines developed (see the companion paper, "Creating Markets for New Vaccines: Part I: Rationale"). They would not require any expenditure unless and until vaccines were developed.

This paper addresses the many design issues that would arise in establishing such programs. It focuses on the design of a vaccine purchase commitment, but much of the analysis carries over to the analysis of tax credits and a World Bank loan fund. Policymakers considering establishing such programs face a host of questions. How can commitments be made credible to vaccine developers? How should eligibility of candidate vaccines be determined? What prices

should be paid for vaccines, and should these prices vary with vaccine characteristics? If multiple vaccines are developed, which should be purchased? Should recipient countries provide co-payments, and if so, how much? How cost effective would such programs be?

If potential vaccine developers are to invest in research, they must believe that once they have sunk funds into developing a vaccine, the sponsors of a vaccine purchase program will not renege on their commitments by paying a price that covers only the cost of manufacturing, and not research. Section 1 of this paper discusses factors affecting the credibility of a vaccine purchase commitment. Courts have held that similar public commitments to reward contest winners or to purchase specified goods constitute legally binding contracts and that the decisions of independent parties appointed in advance to adjudicate such programs are binding. This suggests that if programs contain appropriate legal language, the key determinant of their credibility will not be whether funds are physically set aside in a separate account, but the rules determining eligibility and pricing, and the procedures for adjudicating decisions under these rules. If potential vaccine developers are to invest in research, they must be confident that the adjudicators will not abuse their power. The credibility of a vaccine purchase commitment can be enhanced by clearly specifying eligibility and pricing rules, insulating decision makers from political pressure through long terms of service, and including former industry officials on the adjudication committee.

Section 2 argues that requiring countries that receive vaccines to provide co-payments in exchange for vaccines will give countries incentives to carefully investigate whether candidate vaccines are appropriate for their local conditions. Moreover, for any fixed level of donor contributions, requiring co-payments gives potential vaccine developers greater incentives to conduct research.

Section 3 outlines a possible process for determining vaccine eligibility and pricing. Candidate vaccines would first have to meet some minimal technical requirements, which would ordinarily include clearance by a regulatory agency, such as the U.S. Food and Drug Administration (FDA). They would then be subject to a market test: Nations wishing to purchase vaccines would need to provide a modest co-payment tied to their per capita income and spend down an account assigned to them within the program. Any vaccine meeting these requirements would be eligible for purchase at some base price. Vaccines exceeding these minimum requirements could potentially receive bonus payments tied to vaccine effectiveness.

Section 4 discusses procedures if multiple vaccines are developed for a single disease. The developer of the first vaccine against a disease creates enormous social benefits. Developers of subsequent vaccines create benefits only to the extent that their vaccines are superior or serve populations that are not served by the first vaccine. This suggests that rewards should be greatest for the first vaccine developer. The U.S. Orphan Drug Act specifies that the first developer has market exclusivity unless a subsequent product is clinically superior. This provision is generally believed to account for the Act's success in increasing research on orphan drugs. An analogous provision could grant market exclusivity for purchases under the program to the first vaccine developed unless subsequent vaccines were clinically superior.

Section 5 discusses vaccine pricing and coverage. Research and development on vaccines is typically very expensive, but manufacturing additional doses is usually reasonably cheap. Given total revenue from a vaccine, research incentives are likely to be fairly similar if few doses are sold at a high price, or many doses are sold at a lower price. This suggests that it is efficient to pay per immunized child, rather than per dose, and to include countries and demographic groups in the program as long as vaccination is cost-effective at the incremental

cost of producing additional doses (rather than at the average price per person immunized paid under the program.) The total market promised by the program should be large enough to induce substantial effort by vaccine developers, but less than the social value of the vaccine. A rough rule of thumb in the industry is that a \$250 million annual market is needed to motivate substantial research. A program in which donors provide approximately \$250 million in average annual contributions and co-payments average another \$86 million annually would cost approximately \$10 per year of life saved. The World Bank has termed health interventions costing less than \$100 per year of life saved as highly cost effective [World Bank, 1993].

One way to avoid either paying more than necessary for a vaccine or offering too little to stimulate research would be to offer a relatively modest price initially, and if this price proved insufficient, to raise the promised price gradually until it proved sufficient to spur vaccine development. As long as the price did not increase at a rate substantially greater than the interest rate, vaccine developers would not have incentives to withhold vaccines from the market in hopes of obtaining a higher price. It is unlikely that vaccines for all three diseases would be developed simultaneously, but if donors wished to limit their potential liability, they could cap their committed annual expenditure.

Section 6 discusses the appropriate scope of vaccine purchase commitments. Should the program be limited to vaccines, or also include drugs? Which diseases should be covered?

The conclusion briefly considers the politics of programs to improve vaccine markets. It then discusses the proposed U.S. and World Bank programs and how a private foundation could participate in a purchase commitment program.

This paper builds on earlier work. The idea of an HIV Vaccine Purchase Program was discussed in WHO [1996], and advocated by a coalition of organizations coordinated by the

International Aids Vaccine Initiative (IAVI) at the 1997 Denver G8 summit. Since then, the idea has been explored by the World Bank AIDS Vaccine Task Force [World Bank, 1999, 2000]. Kremer and Sachs [1999] and Sachs [1999] have discussed such programs in the popular press. This paper also draws on earlier work on vaccines, including Batson [1999], Dupuy and Freidel [1990], Mercer Management Consulting [1998], and Milstien and Batson [1994], and on the broader academic literature on research incentives, including Guell and Fischbaum [1995], Johnston and Zeckhauser [1991], Lanjouw and Cockburn [1999], Lichtmann [1997], Russell [1998], Scotchmer [1997], Shavell and van Ypersele [1998], and Wright [1983].

## **1. The Credibility of Vaccine Purchase Commitments**

For a vaccine purchase commitment to be effective in spurring new research, potential vaccine developers must believe that once they have sunk money into producing a vaccine, it will be purchased at a price that covers their risk-adjusted costs of research, as well as their manufacturing costs. Sub-section 1.1 notes that courts have held similar commitments to be legally binding contracts and argues that as long as the sponsor of a commitment has sufficient funds to fulfill the commitment, physically moving money to a separate account is unnecessary to provide legal commitment. Sub-section 1.2 discusses some of the issues that would need to be addressed in specifying eligibility and pricing rules based on technical characteristics of a vaccine. Sub-section 1.3 argues that some discretion will be needed to interpret how general eligibility and pricing rules apply to any specific candidate vaccine, and discusses how the credibility of adjudicating institutions could be enhanced.



## 1.1 Legal Doctrine

This section argues that a suitably designed commitment will be interpreted by the courts as a legally binding contract, and that hence the key credibility issue will not be outright default by the program sponsor, or whether money is physically set aside in a separate vaccine purchase fund, but rather questions over the interpretation of program rules.

Courts have ruled that publicly advertised contests are legally binding contracts [Morantz, 2000]. As summarized in Sullivan [1988], sponsors of contests are contractually obligated to pay the winners according to their public announcements. A contestant who performs the requested act has formed a valid and binding contract with the promoter. Attempts to escape liability by changing contest rules after a contestant has accepted the offer by performing the desired act are generally treated as breach of contract. Advertisements with certain specifications (identification of good, definite quantity of good, etc.) for the purchase of goods at specified prices have also been found to be legally binding. (See Vaccaro [1972] for a summary and analysis of doctrine.)

Moreover, if the procedures in a contest stipulate who will judge the contest, decisions made by the stipulated judge of the contest are usually treated as conclusive [Morantz, 2000]. The majority view among courts is that judges' decisions are conclusive as long as they are made in good faith, although some cases find that contracts giving one party the unilateral right to decide disputes are unenforceable. When the judge of the contest is an independent party, the courts almost universally hold the decision as final unless the decision was made in bad faith, or the judges exceeded the authority specified in contest rules.<sup>1</sup>

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<sup>1</sup> The credibility of the vaccine purchase commitment can be increased by framing it as a unilateral contract (i.e., one not requiring a promise by others to become valid) and explicitly including a promise not to revoke. Some

There are a number of precedents for programs to reward developers of new technologies. The British government established a £20,000 prize for a method of determining longitude at sea after a fleet got lost and struck rocks, drowning 2,000 sailors. The prize was won by John Harrison for the chronometer.<sup>2</sup> More recently, the Kremer prize for human-powered flight led to the historic flight of the Gossamer Albatross across the English Channel [Grosser, 1991]. The \$30 million “golden carrot” contest for an energy efficient refrigerator sponsored by 24 U.S. electric utilities offered to pay the winning team a certain amount for every unit sold. Whirlpool won the contest with a line of refrigerators that operated 70 percent more efficiently than 1992 federal requirements.

Given that legally binding contracts can be written, physically setting aside funds in an escrow account is not necessary for a commitment to be binding, as long as the sponsor of a vaccine purchase commitment has sufficient funds to fulfill the commitment. The key questions for credibility revolve around specifying eligibility and pricing rules and procedures for adjudicating disputes under these rules.

Depending on legal language, commitments could be made more or less binding. The options range from a simple announcement of an intention to purchase vaccines, to a legally binding announcement with details on eligibility and pricing. The more binding the commitment, the stronger the incentives for potential vaccine developers. In general, there is a tradeoff between flexibility and credibly committing to pay for a vaccine. Imperfect commitment reduces both the expected revenue for vaccine developers and expected costs for

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additional legal issues might arise if a purchase commitment were made by a national government or an international institution, and legal research would be needed to address these issues.

<sup>2</sup> Sobel [1995] argues that the longitude prize committee was biased towards an astronomical solution and insisted on improvements and multiple trials, creating repeated delays, until the king intervened on behalf of the chronometer's inventor. Note, however, that this account is disputed. The economic historian Paul David argues that the conditions imposed by the committee were reasonable [Personal communication, 2000]. In any case, this points to the importance of program rules and adjudication procedures in influencing credibility of purchase

the sponsor in the same proportion. It reduces efficiency to the extent that the parties are risk averse.<sup>3</sup>

## 1.2 Issues to Consider in Determining Eligibility and Pricing

A program to increase the market for vaccines could offer to purchase vaccines meeting certain technical specifications, offer to match money spent on vaccine purchases by other institutions, or use some combination of these approaches. For example, the Kremer prize laid out detailed technical eligibility requirements. The U.S. tax credit proposal does not specify detailed technical requirements, other than FDA approval, but merely states that a 100 percent tax credit will be given for sales of vaccines to non-profits and international institutions, which would presumably make their own judgments as to whether candidate vaccines are acceptable.

The following are some of the key issues which would need to be considered in determining vaccine eligibility and pricing based on technical specifications.

- vaccine efficacy—the reduction in disease incidence among those receiving the vaccine.<sup>4</sup> Efficacy might vary in different circumstances. A vaccine could

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commitments.

<sup>3</sup> For example, consider a simple case in which potential vaccine developers seek to maximize expected profits and accurately interpret the degree of commitment entered into by potential donors. Suppose that in the absence of a particular piece of contractual language in the vaccine purchase commitment, there is a 90 percent chance the sponsor purchases the vaccine at the promised price and a 10 percent chance that they renege and renegotiate to a price of half the level originally promised. In this case, in the absence of a contractual arrangement, firms which seek to maximize expected profits will act as if the value of the program is not the promised annual revenue from the program, but rather 95 percent of the promised annual revenue. Note that while the expected incentive is only 95 percent of the promised level, so is the expected cost to the sponsor. To the extent that both vaccine developers and the sponsor are risk-averse, they would both prefer a perfectly credible commitment of \$950 million to a 90 percent chance of \$1 billion and a 10 percent chance of a \$500 million payment. In this sense, imperfect credibility reduces the efficiency of purchase commitments.

<sup>4</sup> Some have speculated about the possibility of an “altruistic” malaria vaccine, which would block further transmission of the disease, without protecting the person who takes the vaccine. It is unclear how many people would be willing to take such a vaccine. Moreover, given the high intensity of malaria transmission in many parts of Africa, the epidemiological impact of an altruistic vaccine might be quite small unless the vaccination rate was

potentially be more efficacious against some strains of the disease than others, and thus be better suited to some geographic areas than others. It could work for some age groups, but not others. A vaccine might prevent severe symptoms of the disease, but not prevent milder cases.

- the number of doses required, the efficacy of the vaccine if an incomplete course is given, and the ages at which doses must be taken. If too many doses are required, fewer people will bring their children in to receive the full course of immunization. If the vaccine can be given along with vaccines that are already widely administered, delivery will be much cheaper.
- vaccine side effects. Side effects could differ for different sub-populations. Side effects would also need to be considered for people who do not comply perfectly with the delivery protocol. For example, taking a partial course of a malaria vaccine could potentially interfere with natural limited immunity.
- the time over which the vaccine provides protection, and whether booster shots could extend this period;
- what level of rigor would be required in the field trials. For example, how long would subjects have to be followed to determine the length of protection? How many separate studies in different regions would need to be conducted to assess efficacy against different varieties of the disease?
- the extent to which vaccines would lose their effectiveness over time.

Presumably, some ongoing monitoring of vaccine effectiveness in the field would

be required, and if it appears that resistance to the vaccine is spreading, vaccine purchases would have to be reassessed.

One possibility would be to design eligibility requirements based on rules using these criteria in such a way that vaccines would be considered eligible if they met a cost-effectiveness threshold.<sup>5</sup> Eligibility and pricing rules could potentially be set so that vaccines meeting a certain cost-effectiveness threshold would be eligible for purchase and vaccines exceeding this threshold would receive higher prices.

Note, however, that mis-specifying eligibility and pricing rules could misdirect research incentives away from appropriate vaccines, or vitiate research incentives altogether. For example, if the program failed to specify otherwise, it might be obligated to purchase a malaria vaccine that interfered with the development of natural immunity and provided only temporary protection. Such a vaccine might merely postpone malaria deaths. If such a vaccine were eligible for purchase under the program, researchers might pursue it, rather than devoting their efforts to more useful lines of research. On the other hand, there is a risk that the program could set specifications so stringent that they would be difficult to achieve. This would discourage pharmaceutical firms from following promising leads. For example, if the specifications required 90 percent efficacy against all strains of the disease, potential vaccine developers might not pursue a candidate vaccine that would be likely to yield 99 percent protection against most strains, but only 85 percent protection against others. If it were difficult to create a vaccine delivering 90 percent protection in all regions, no vaccine at all might be developed.

Aside from specifying eligibility rules, the program would have to specify pricing rules. Paying more for superior vaccines might create more appropriate incentives for researchers. A

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<sup>5</sup> In future work, Rachel Glennerster and I plan to use the techniques in Appendix 2 to examine the cost-effectiveness of vaccines with different degrees of efficacy, requiring different numbers of doses, and providing

90 percent efficacious vaccine is worth more than an 80 percent efficacious vaccine, and a vaccine that requires no booster is worth more than one requiring boosters every five years.

### **1.3 Procedures to Increase Credibility of a Vaccine Purchase Commitment**

General eligibility and pricing rules could be set out, but someone would have to exercise discretion in interpreting these rules once vaccines have been developed and tested.<sup>6</sup> Once the vaccine developer has sunk hundreds of millions of dollars in research, adjudicators might be tempted to offer a price that covered only manufacturing costs or to insist on excessive product testing and improvements. If pharmaceutical executives suspect that the adjudicators will succumb to these temptations, the companies will be reluctant to invest in a vaccine.

Credibility of vaccine purchase commitments to potential developers could be enhanced by appointing appropriate decision makers (such as a committee with some members who have worked in the pharmaceutical industry), insulating decision makers from political pressures through long terms of service, establishing a minimum purchase price, and placing limits on the discretion used by the program committee by laying out reasonably transparent rules for determining eligibility and pricing. Another way to enhance the credibility of a commitment is to establish a program that covers a number of different diseases which primarily affect

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different lengths of protection.

<sup>6</sup> Setting efficacy requirements for eligibility for an HIV vaccine is particularly difficult. Because of the key importance of a core group of high-risk people in influencing the spread of HIV, even a vaccine of low efficacy may prove useful in disrupting the chain of transmission if it is targeted to this group. On the other hand, at least theoretically, an imperfectly effective HIV vaccine could increase the spread of HIV, since people might adopt riskier behaviors if they felt they had reduced the chance of infection by taking an imperfect HIV vaccine. This outcome seems unlikely, however, since in steady state, an imperfectly effective vaccine could also potentially make the highest activity people more hopeful about their chances of being uninfected, and therefore less likely to adopt risky behavior. Delivery of an HIV vaccine may have to use very different channels than delivery of existing childhood vaccines, particularly if it is targeted to such a core group. Little is known about the costs of reaching such groups.

developing countries. The program would then have an incentive to build up a reputation for fair play.<sup>7</sup>

The experience of central banks may offer some lessons for the design of a vaccine purchase program. Just as a vaccine purchase program would need to make a credible commitment to purchase an effective vaccine if one were developed, central banks need to head off inflationary expectations by credibly promising to take tough action if inflation starts to increase. Central banks insulate decision makers from political pressures by appointing them for long terms, and a vaccine purchase program could do the same. Appointing central bankers with strong anti-inflation credentials also helps build credibility for central banks. Similarly, delegating decisions regarding eligibility and pricing to a committee which included some members who had worked in industry might help convince potential vaccine developers that the committee would not impose unreasonable conditions after they developed a vaccine.<sup>8</sup>

Commitments by the vaccine purchase program will be more credible if the program administrators have incentives to build a reputation for fulfilling promises. If the program covered vaccines against several diseases, program administrators would have incentives to

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<sup>7</sup> Note that the problem of inducing firms to conduct research and development on vaccines for which they expect the government to be the major purchaser is in some ways similar to the problem of inducing firms to conduct research and development on weapons for which they expect governments will be the major purchaser. In each case, the government must convince the firms contemplating undertaking research that it will not take advantage of them by insisting on low prices once they have already sunk their investments in research. Procurement rules for the U.S. Department of Defense do not instruct procurement officers to purchase orders at the lowest possible price, but instead to purchase at a price that covers suppliers' costs. The formulas used for calculating costs typically allow firms to cover more than manufacturing costs, which in turn provides an incentive for firms to invest in research and development to produce attractive products that allow them to win procurement contracts. Rogerson [1994] suggests that this serves as a reputational mechanism for encouraging research by defense contractors. The Defense Department has an advantage in that it is a long-standing institution, with a well-developed reputation about how it treats contractors, and contractors can count on the desire of the Defense Department to maintain a reputation for the future, because the continued existence of the Defense Department seems assured. Unfortunately, the long-term future of a vaccine purchase program is less certain.

<sup>8</sup> Unfortunately, there is a history of antagonism between the pharmaceutical industry and existing international vaccine purchasers such as the Pan American Health Organization (PAHO) and the United Nations' Children's Fund (UNICEF), which have a culture of trying to purchase vaccines at the minimum possible price. These institutions, therefore, might have difficulty administering a program designed to increase private-sector incentives for vaccine development.

develop a reputation for treating vaccine developers fairly, so as to build credibility with potential developers of other vaccines.<sup>9</sup> Nonetheless, it may take time to develop a reputation.

One way to help build credibility with potential vaccine developers would be to set a minimum price in advance.<sup>10</sup> This could help solve the time-consistency problem, but at some cost. A vaccine which is useful, but not useful enough to warrant purchase at the minimum guaranteed price, would not be purchased at all. In practice, however, this problem may not be that serious. Most vaccines that passed regulatory approval would be cost-effective at even a high price per person immunized relative to the likely availability of funds (See Appendix 2). This is because vaccines falling far short of U.S. or European regulatory requirements have great difficulty winning wide approval in developing countries in any case.<sup>11</sup> If one takes as given that vaccines will only be used if they meet a stringent risk-benefit ratio, it seems quite unlikely that guaranteeing a minimum price *ex ante* would lead to rejection of an otherwise usable vaccine on cost-effectiveness grounds. If a vaccine were not useful enough to warrant purchase at a few dollars per person immunized, the cost of failing to purchase it would not be that great. Moreover, if a vaccine turned out to be socially useful, but not good enough to qualify for purchase under the program at the promised price, this would not preclude individual countries from purchasing the vaccine or other donors from purchasing it. The costs of guaranteeing a minimum price seem small relative to the benefit of improving the credibility of commitments to

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<sup>9</sup> On the other hand, if the program maintained a single fund which could be used to purchase vaccines for any of several different diseases, then potential vaccine developers might fear that once they had invested money in developing a vaccine, the vaccine purchase program would try to pay a very low price for the vaccine, hoping to save its resources to purchase vaccines for other diseases. This problem could be addressed by maintaining separate funds (or making separate financial commitments) for different diseases.

<sup>10</sup> Setting low prices is the most likely way that the program could take advantage of vaccine developers. Program adjudicators concerned with public health will have limited incentives to insist on further trials, for example, because they will presumably want to get an effective vaccine into the field.

<sup>11</sup> This is illustrated vividly by the apparently meager prospects of the Wyeth-Ayerst rotavirus vaccine in developing countries after it was withdrawn from the U.S. market following evidence that it causes intussusception in rare cases. The benefits of the vaccine are likely to outweigh by far its risks in developing countries, where rotavirus



reward vaccine developers, and thus spurring research.

## 2. Co-Payments

Another way to increase the market for vaccines would be to offer to match vaccine purchases by others. This is similar, in effect, to purchasing the vaccine and providing it to others in exchange for a co-payment. Requiring countries receiving vaccines to provide reasonable co-payments can boost incentives for vaccine developers given any fixed level of donor contributions. Co-payments also help ensure that the authorities in recipient countries feel that the vaccine is suitable for use in their circumstances. This is important since conditions vary among countries. For example, a vaccine might be effective against the strains of malaria prevalent in some countries, but not against other strains. Finally, requiring co-payments is a useful test of a country's commitment to a program. If a country is prepared to make a co-payment, it is also more likely to be prepared to take the other steps necessary to ensure that the vaccine is delivered to the people who need it.

Setting the level of co-payments involves a tradeoff between improving access once a vaccine has been developed and creating incentives for vaccine development. On the one hand, once a vaccine has been developed, it will be produced at the efficient scale if the co-payment equals the marginal cost of producing an additional dose. On the other hand, given a fixed level of donor contributions, incentives for vaccine development will be greater if developing countries provide co-payments at their willingness to pay for the vaccine.

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kills three-quarters of a million children each year. Nonetheless, it appears unlikely that the vaccine will ever be widely used.

Setting co-payments from countries receiving vaccines just below their estimated willingness to pay for vaccines will maximize incentives for vaccine development while not reducing consumption of vaccines below the optimal level. Since richer countries are likely to be willing to pay more for vaccines than poorer countries, this implies that co-payments should rise with per capita income.<sup>12</sup> Willingness to pay may also be greater for diseases that create a particularly high health burden, such as HIV/AIDS. Given the uncertainty in estimating this willingness to pay and the need for a uniform co-payment policy across heterogeneous countries, it makes sense to estimate willingness to pay conservatively. Insisting on too great a co-payment would limit access to the vaccine, and, by reducing take-up, would reduce incentives for vaccine developers.

Note also that setting the required co-payments close to countries' willingness to pay reduces vaccine developers' temptation to try to extract supplemental payments from purchasing countries. It is not clear whether the vaccine purchase program should agree to be a party to vaccine purchases with supplemental co-payments greater than those required under the program, even if the recipient country agrees to this. Allowing supplemental payments broadens the scope for vaccine developers to demand prices greater than those offered under the vaccine purchase program, and these higher prices could potentially exclude some countries from access to vaccines. For example, if the vaccine developer felt that most countries would be willing to supplement the required co-payment by \$1 a dose, it might demand this from every country. Those countries unable to afford this supplemental payment would not be able to obtain the vaccine.

Note that tying co-payments to income achieves many of the benefits of tiered pricing. If co-payments are set appropriately, access to vaccines is expanded so that vaccines can be used wherever the social value of the vaccine exceeds the marginal production cost. Incentives for

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<sup>12</sup> Willingness to pay is also likely to be higher for countries with a greater burden of disease, but requiring a larger co-payment from countries with a greater disease burden seems inequitable and is likely to be politically infeasible.

vaccine development can correspond to the aggregate willingness to pay for vaccines. Yet vaccine developers need not take the politically damaging step of revealing their willingness to produce additional doses at low cost, thus risking generating enhanced political pressures for price regulation.

### **3. Combining Technical Requirements and a Market Test**

Technical eligibility requirements could potentially be combined with a market test. For example, candidate vaccines could first be required to meet basic technical requirements, which would typically include clearance by some regulatory agency (such as the U.S. FDA). They could then be required to meet a market test—developing countries wishing to purchase vaccines using program resources would be required to contribute a co-payment, and would be required to draw down an account they would have within the vaccine purchase program. Any vaccines meeting these requirements would be eligible for purchase at some base price. Vaccines exceeding these requirements could potentially receive bonus payments linked to vaccine effectiveness. Ideally, this would make commitments to purchase useful vaccines at remunerative prices credible to potential vaccine developers, but would leave enough flexibility that appropriate purchasing decisions could be made after vaccines had been tested and their characteristics became known.

#### **3.1 Basic Technical Requirements**

To be eligible for purchase, vaccines could be required to fulfill basic technical requirements, which would normally include regulatory clearance by an established regulatory

agency, such as the U.S. FDA or its European counterpart. This would ensure that the funds were spent for *bona fide* vaccines, rather than for quack remedies. However, a vaccine may pass a risk-benefit assessment in one country, but not another. For example, a malaria or tuberculosis vaccine with significant but small side effects might not be appropriate for general use in low-prevalence countries, such as the United States, but might save millions of lives in high-prevalence areas.

It might make sense to allow the program, at its discretion, to waive the requirement of regulatory approval in donor countries if a country requested the vaccine and a scientific committee established by the program concurred that the vaccine satisfied the risk-benefit assessment given the situation in the applicant country. More generally, it might be appropriate to guarantee that any candidate vaccine satisfying certain high technical standards would receive automatic approval to go on to the market test. There could also be a gray area, in which candidate vaccines could be approved at the discretion of a scientific committee. This would provide assurance to potential vaccine developers that if they develop a high-quality vaccine, they will have a market. It would also allow the committee the flexibility to consider purchasing vaccines that passed a risk-benefit analysis, but fell short of an ideal vaccine.

Just as a vaccine might satisfy a risk-benefit assessment in a high-prevalence country, but not in the United States, is possible that a vaccine could be appropriate in the United States, but not elsewhere. For example, a malaria vaccine that interfered with natural immunity might be appropriate for U.S. travelers, who would not have built up this immunity in any case, but not for long-term residents of malarious areas. A few minimal technical requirements beyond regulatory approval are therefore likely to be appropriate before vaccines were made eligible for the market test described below. Travelers' vaccines for malaria, which protect people making

short trips, would presumably be ineligible.<sup>13</sup> Other technical requirements might include a requirement that a vaccine could only be purchased for a country if it had been shown effective for the strains of disease prevalent in that country. Vaccines requiring more than some cutoff number of doses to be effective might require a special waiver for eligibility. Some ongoing monitoring might be required, to ensure that resistance to the vaccine had not developed and spread. However, the credibility of purchase commitments with potential vaccine developers would be enhanced by keeping technical eligibility requirements beyond regulatory clearance minimal and clearly defined to reduce the potential for abuse of discretion. This would decentralize the basic purchasing decision to individual recipient countries. Of course, these countries would be free to consider recommendations put out by the World Health Organization or any other body.

### **3.2 The Market Test**

As discussed above, vaccines could meet regulatory approval, but still be unsuitable for widespread use in a particular developing country. For example, a vaccine that was effective only if people received ten precisely timed doses might be useful for the U.S. military, but not for most people in developing countries. Requiring vaccines which satisfy the technical criteria to meet a market test would allow purchasers the flexibility to make decisions about whether a particular vaccine is appropriate for their needs. In particular, developing countries would have incentives to seriously consider the suitability of candidate vaccines if they had to provide a co-

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<sup>13</sup> It might therefore, for example, be appropriate to specify that the program could require proof of efficacy over some extended period for sporozoite malaria vaccines.

payment and draw down an account within the vaccine purchase program that would be established specifically for each country.

Co-payments help ensure that after a particular vaccine has been tested, it is considered worth purchasing. However, co-payments alone may not be sufficient to demonstrate country commitment, since donors might offer to help fund co-payments. It is not clear that it would be possible or desirable to prohibit this.

Countries could be further motivated to carefully consider their purchases by establishing sub-accounts within the program for each country. If a country decided to purchase a vaccine, it would draw down the commitments allocated to it. This system would give countries an incentive to purchase a vaccine only if they were confident that it could be effectively administered in their country and if they did not expect a superior vaccine to come on the market shortly. Otherwise, they would be better off saving the funds in their sub-account.

In the absence of separate sub-accounts, countries might agree to purchase even marginally effective vaccines, knowing that if they did not consume the available funds, other countries would. If potential vaccine developers anticipated this, they might invest in a candidate vaccine that looked like it would meet only minimal eligibility requirements, rather than investing in a slightly more risky, but ultimately much more promising, vaccine. If countries must spend funds earmarked for their own vaccine purchases, they will have more incentive to purchase only high-quality vaccines, thus providing incentives for potential vaccine developers to focus on developing such vaccines. Since countries would not be able to use their accounts to purchase anything but vaccines, and would not receive interest on their accounts if

they remained unspent, they would have every incentive to use their accounts to purchase a good vaccine if one were available.<sup>14</sup>

Relying only on a market test and eliminating any technical requirements could potentially lead to the purchase of inappropriate vaccines due to bribery or tied deals. Vaccine developers could offer to kick back some percentage of the purchase price to the developing country in the form of price reductions on other pharmaceuticals, or even bribes. This could potentially be an attractive arrangement for the developing country or its officials, since the country itself would contribute only a co-payment towards the cost of the vaccine, with the bulk of the financing coming from the vaccine purchase program.

A series of safeguards are therefore needed to prevent purchase of inappropriate vaccines due to bribery or tied deals. The technical requirements for eligibility provide the first and most important line of defense. This would prevent a country from using program funds to purchase a quack vaccine manufactured by a politically-connected firm. Outright corruption could probably be limited with provisions punishing firms found guilty of bribing officials and restricting the amount of travel, training, and other perks that vaccine sellers could provide to health ministry officials. Under the U.S. Foreign Corrupt Practices Act, firms and executives found guilty of bribing foreign governments are subject to criminal prosecution. Other nations are now adopting similar laws. Since the developing-country vaccine market is a small part of overall business for most large pharmaceutical companies, they would likely be reluctant to risk bad publicity, the attention of regulators, and legal sanction in order to make some extra money on vaccines.

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<sup>14</sup> If interest were paid on accounts, countries would be under less time pressure to reach agreement with vaccine developers, and therefore might have such a strong bargaining position that they could prevent vaccine developers from recovering their research costs. Note that vaccine developers are automatically under time pressure to reach a deal with purchasers, because their patent is time-limited. Moreover, if interest is not paid on individual country accounts, then any interest accumulated on the program could be used to fund grants for basic vaccine research, or allocated to countries where disease prevalence had increased since the program was established.

Whistle-blower procedures could be instituted to protect, or even reward, committee members reporting attempts at bribery by vaccine developers. Similarly, vaccine developers could blow the whistle on committee members who tried to insist on kickbacks. Members of the committee who were proven to have asked for kickbacks could be removed from the committees.

Implicit tied dealings are more difficult to regulate. A pharmaceutical firm simultaneously negotiating with a health ministry over a malaria vaccine and an antibiotic might convey to the ministry that it would be willing to be flexible on the antibiotic price if the ministry would purchase the malaria vaccine. In the absence of further incentives, vaccine developers might therefore aim only at creating a vaccine that could pass minimal eligibility requirements, rather than a more widely useful vaccine.<sup>15</sup>

One way to limit corruption and tied deals, while still preserving a market test, would be to include civil society as well as governments in countries' decision-making processes. For example, the committee making purchase decisions for a country might include not only representatives of the Ministry of Health, but also respected physicians, non-governmental organization representatives, and scientists. Countries wishing to participate in the program could be required to set up such committees in advance, and members could have security of tenure. Some members of the committee could be appointed by the vaccine purchase program. The committee could have authority to release resources from the country's sub-account within the program. The government would need to authorize disbursements of public funds to cover co-payments, but donors could potentially fund co-payments.

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<sup>15</sup> Payments by third parties are also difficult to regulate. Suppose a Swiss firm invents a malaria vaccine which is not effective against the strains of malaria prevalent in some country, and therefore is not appropriate for that country. The government of Switzerland or a foundation supported by the firm could provide aid for purchasers to use towards their co-payments. With a 20 percent co-payment, this would allow the government of Switzerland or the foundation to spend one dollar to raise five dollars for the company.



Limiting the number of doses purchased for any one country would limit the potential loss from tied deals and corruption. The number of doses purchased for a country might be limited to the number needed for the annual birth cohort, with some adjustment for the initial years of the program when a backlog of unimmunized people would need to be vaccinated.

### **3.3 Bonus Payments Based on Vaccine Quality**

Specifying a minimum price which would be paid for vaccines meeting the first two steps – technical requirements and the market test -- would help provide potential developers with a credible commitment. However, it would be desirable for developers to have incentives to develop vaccines that exceed a minimum eligibility threshold. It might therefore be useful to provide bonus payments depending on vaccine quality. One standard way to measure cost-effectiveness in health is the cost of saving a Disability-Adjusted Life Year, or DALY. DALYs take into account not only the years of life lost but also the years of disability caused by a disease. In order to create appropriate incentives for vaccine developers to develop high-quality vaccines, bonus payments could be set so as to tie the reward to the number of lives or DALYs saved and to the cost of delivery.

Bonuses could be provided for vaccines believed to exceed a cost-effectiveness threshold, in dollars spent per DALY averted. If a vaccine exceeded this threshold, some fraction of the resulting savings could be returned to the vaccine developer as a bonus above the base price.

Basing incentives on lives or DALYs saved would create good incentives for pharmaceutical firms to develop vaccines that create positive externalities, such as a malaria vaccine with an altruistic component which kills gametocytes, and thus prevents other people

from becoming infected. Any side effects of a vaccine could be subtracted from the measure of lives or DALYs saved.<sup>16</sup>

Bonuses could also be paid if the vaccine was cheap to deliver. This would create incentives for researchers to develop vaccines that are oral, rather than injectable, that do not require many doses, and that can be delivered along with the vaccines currently given as part of the Expanded Program on Immunization (EPI).

Bonus payments could potentially be set in two ways. A committee could be free to base bonus payments directly on its estimates of the number of lives or DALYs saved by a particular vaccine, using any data it wished.<sup>17</sup> Alternatively, a schedule of bonus payments could be set in advance as a function of more easily measured vaccine characteristics, such as efficacy in clinical trials, the number of doses needed, etc. The approach used in Appendix 2 could be extended to estimate the set of vaccine characteristics associated with any particular cost-effectiveness threshold.

Directly estimating DALYs or lives saved after vaccines are developed allows the program to consider a broad range of vaccine characteristics and to use up-to-date information,

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<sup>16</sup> It is worth noting that currently, the medical profession and society as a whole seem to weight DALYs caused by side effects much more heavily than DALYs saved.

<sup>17</sup> Information about the number of lives or DALYs saved might become available only gradually, and therefore, if this approach were adopted, it might theoretically be best to condition payments on long-run outcomes. For example, it might initially be unclear whether a vaccine provides protection only temporarily, or indefinitely. The extent to which a vaccine prevents secondary infections might also be difficult to predict in advance. Initial bonus payments to vaccine developers could be based on conservative estimates of lives or DALYs saved and additional payments could be made later, depending on the realization of lives or DALYs saved. Of course, if payments were delayed, accumulated interest would have to be paid as well. Basing bonus payments to vaccine developers on realized DALYs or lives saved, rather than on the results of the clinical trials required for regulatory approval, creates better incentives to develop vaccines that will work in the real world, rather than only in clinical trials, where it is easier to make sure that delivery protocols are followed exactly. Moreover, if bonus payments could be claimed after a vaccine had already been used, it would be much more difficult for a price-setting committee within the vaccine purchase program to refuse to pay a remunerative price. Before a vaccine is used in the field, the committee could argue that it deserves only a small bonus, citing potential problems with the vaccine. However, if the vaccine is used, and it reduces the burden of malaria by 90 percent, it will be very hard for the committee to argue that it is ineffective. (Exceptions to this are new diseases, such as HIV, for which predictions of prevalence in the absence of a vaccine are likely to be particularly inaccurate.)

but it also creates more uncertainty for vaccine developers and raises the prospect of bias by the committee charged with estimating DALYs and costs.<sup>18</sup> The appropriate strategy depends in part on how trustworthy the committee charged with these tasks is considered to be, and in part on what reasonably transparent and objective procedures can be developed for measuring vaccine efficacy. Thus, it may vary among diseases.<sup>19</sup>

Basing payments directly on the number of lives or DALYs saved through a vaccine, and the cost of delivery, is also potentially problematic because these quantities depend not only on actions under the control of the vaccine developer, but also on actions by others. To the extent that health ministries cannot easily maintain cold chains or deliver vaccines to rural areas on a precise schedule, vaccinations that require cold chains and precisely timed deliveries will be expensive per life or DALY saved.

If the weaknesses of health ministries are not strategically aimed at extracting payments from the vaccine developer, this will create appropriate incentives for vaccine developers. Vaccine developers should try to design vaccines that are appropriate for actual health systems, not for some theoretical ideal health system. For example, if health ministries cannot maintain cold chains for vaccines, then vaccine developers should have incentives to develop heat stable vaccines.

However, to the extent that health ministries behave strategically, it will be best to base bonus payments on preset indicators of the likely number of DALYs saved, rather than the actual number of DALYs. This is because if vaccine developers were paid based on realized DALYs

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<sup>18</sup> Basing incentives on mortality rather than DALYs might be attractive, since mortality is easier for the public to understand and perhaps less subjective and open to manipulation. On the other hand, it may be best to more closely tie incentives to objectives by rewarding DALYs saved. It is desirable to give researchers incentives to reduce morbidity as well as mortality, and to guard against side effects that cause morbidity.

<sup>19</sup> For example, in Africa, HIV prevalence can be taken as a good indicator of future HIV deaths and disability, but prevalence of malaria may be a poor indicator of the total burden of malaria, since a vaccine might greatly reduce malaria mortality without preventing infection.

saved, health ministries could potentially try to extract payments from the vaccine developer in exchange for agreeing to distribute the vaccine efficiently. This would weaken incentives for vaccine development.

If the committee charged with estimating lives or DALYs saved simply makes honest mistakes in calculating these quantities, but those mistakes do not systematically tend to underestimate or overestimate the actual effects of the vaccine, then the potential profit from developing a vaccine could as easily be increased or decreased by the uncertainty in calculations of DALYs or lives saved. The attractiveness of investment in vaccines would be reduced, but only to the extent that vaccine developers are not willing to take gambles that could turn out to help them as easily as to hurt them.

Errors in estimation of DALYs or lives saved are particularly problematic if vaccine developers can influence these estimates through actions other than research. For example, if politically-connected pharmaceutical firms obtain more favorable DALY calculations, firms will divert effort towards developing political connections and away from developing good vaccines.

The scope for bias would be reduced by setting forth procedures as fully as possible ahead of time, working under a framework of establishing a bonus per life or DALY saved. The World Health Organization project on the burden of disease has developed detailed procedures for estimating DALY burdens. Epidemiological surveys could be conducted to assess the burden of various diseases prior to the development of vaccines.

### **3.4 Sunset Provisions**

Sunset provisions could be incorporated into a vaccine purchase program. For example, a malaria vaccine fund could revert to the donors or be used for other health problems in developing countries if, after fifty years, no qualifying vaccine had been developed, or if at some earlier time, a scientific committee established by the program determined that the burden of malaria had been sustainably cut more than 50 percent through other techniques, such as insecticides. Sunset provisions could be continuous, so that the purchase commitment would fall with the severity of the disease. Note that any bonus payment based on DALYs or lives saved would automatically fall with prevalence of the disease. A sunset provision would increase the risk borne by potential vaccine developers, but biotech and pharmaceutical firms routinely have to bear the risk that alternative technologies will render the projects they are working on superfluous. There is no reason why this should be any different for firms working on developing country diseases. It is efficient for researchers to consider the possibility that their work will be superseded by other technologies when choosing their research projects.

#### **4. Procedures for Multiple Vaccines**

For vaccine purchase commitments to spur research, it is essential that intellectual property rights be respected. If the program purchases vaccines from imitators, rather than respecting the intellectual property rights of the original developers, incentives for vaccine development will be vitiated.<sup>20</sup>

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<sup>20</sup> If the vaccine purchase program were an international organization, it is not clear what court would have authority to rule on intellectual property rights questions. One option would be to spend funds from each donor in accordance with the intellectual property rights laws of that country. For example, U.S. funds would not be used to purchase vaccines that violate U.S. patents.

However, enforcing patents may not be enough. Once one vaccine for a disease has been developed, it becomes easier for competitors to develop alternative vaccines, even if the first is protected by a patent, as it can be relatively easy to design around vaccine patents. Developers of the initial vaccine, therefore, face a risk that a marginally superior vaccine will be produced shortly after the initial vaccine is developed and that this subsequent vaccine will capture the entire market. This risk may deter research. In many industries, first-mover advantages due to network effect or to brand loyalty by customers are as important as patents in protecting innovations, but since governments are the main purchasers of vaccines, and are less likely to be influenced by brand loyalty, other forms of protection may be needed for vaccine developers.

It will be important to preserve rewards for the initial developer, who will have made the largest investment in research. Currently, the world needs acceptable vaccines for malaria, tuberculosis, and HIV/AIDS, and incentives for a private developer are a small fraction of the social value. Once an adequate vaccine is developed, however, the world's need for a second vaccine will be much more limited. This suggests a smaller reward will be needed to bring private incentives for a second vaccine into line with the social value of a second vaccine. To some extent, the initial developer will receive a larger share of vaccine purchases in any case, since the initial developer will sell vaccines used to immunize the backlog of unimmunized adults, while subsequent developers will be restricted to the market of new cohorts of children. Pricing a vaccine in nominal terms will also disproportionately help the original developer, since real prices will fall over time. (It would even be possible to specify a falling time path of nominal prices.)

The developer of the first vaccine could be further protected through an exclusivity clause similar to that in the Orphan Drug Act. This would require that the initial vaccine be

purchased if newer alternatives were not clinically superior. This provision is widely believed to have greatly increased research on orphan drugs [Shulman and Manocchia, 1997].

In practice, the exception for “clinically superior” vaccines may not weaken incentives for the first developer that much, since regulatory standards for approval of the first vaccine are likely to be high, and it may be difficult to show that a subsequent vaccine is “clinically superior.”

Note that market exclusivity would apply only to the target population for which the original vaccine was adequate. Thus, for example, if one firm develops an AIDS vaccine effective against a particular clade of the disease, it would have marketing exclusivity for that clade, but not for other clades.

One potential objection to the market exclusivity provision is that it could increase the risk borne by developers. In the absence of a market exclusivity clause, if several firms develop vaccines around the same time, they will share the market. Providing market exclusivity to the first vaccine developer could potentially increase risk. On the other hand, to the extent that prices fall if multiple vaccines are invented, or firms dissipate potential profits in marketing expenditures, the expected reward to investing in vaccine research and development is greater with a market exclusivity clause. The success of the Orphan Drug Act in increasing research and development on orphan drugs suggests that the increase in expected profits is the key issue for potential developers. If it were thought important to avoid increasing the risk borne by potential vaccine developers, purchases under the program could be limited to those vaccines invented within some period (perhaps a year or two) following the licensing of the first acceptable vaccine, unless a subsequent vaccine was clinically superior. This would reduce risk for firms

engaged in a tight race to develop a vaccine, while also reducing the chance that “me too” vaccines would greatly reduce sales for the initial developer and thus deter research.

The exception in the Orphan Drug Act’s market exclusivity provision for clinically superior products could potentially be modified for application to a vaccine purchase commitment. Ideally, if a subsequent vaccine were clinically superior, the price paid would be related to the marginal improvement the subsequent vaccine represents over the original vaccine, and the original vaccine developers would continue to receive compensation in line with the social value of their work. A bonus payment system provides a potential mechanism for doing this. One option would be to retain the exclusivity clause even if a superior vaccine were developed, but give the developer of the original vaccine incentives to buy out the technology of the second producer. The bonus payments that would go with supplying a superior vaccine would provide such an incentive. Alternatively, the newer vaccine could be purchased at a price based on its efficacy, but the developer of the newer vaccine could then be required to pay the original developer an amount equal to the price paid for the original vaccine, less an allowance related to the production cost of the new vaccine. While this approach matches private and social research incentives more closely than the blanket exception for superior products in the Orphan Drug Act, it would be difficult to administer.

## **5. Vaccine Coverage and Pricing**

This section first argues that the key determinant of research incentives will be the total revenue generated by a vaccine, rather than the price per person immunized. Decisions about where it is cost-effective to vaccinate should be based on the incremental cost of manufacturing



an additional unit of vaccine, rather than the average price paid per person immunized under the program. Given the desired market size and number of required vaccinations, the price per person immunized can be determined by dividing the desired market size by the number of people needing immunization. The tricky question is determining the appropriate market size. The total market promised should be large enough to stimulate research, but not so large that a vaccine purchase program would not be cost-effective. Sub-sections 5.2 and 5.3 note that a rough rule of thumb in the industry is that a market of \$250 million per year is necessary to spur significant research, and argue that a vaccine purchase program would be highly cost effective even at a substantially larger scale. The sponsor of a vaccine purchase commitment could start with a modest program, which would not be too expensive, but retain the option to increase the value of the program if the original program proved too small to stimulate sufficient research. Sub-section 5.4 argues that as long as the vaccine price is not expected to increase too quickly, this will not lead vaccine developers to withhold a vaccine from the market in the hope of getting a better price.

## **5.1 Coverage**

The key determinant of research incentives will be the total discounted revenue generated by a vaccine. It is very expensive to conduct research, but once research is complete, it is typically fairly cheap to produce additional doses. For a fixed amount of total revenue, vaccine developers will therefore be almost as happy to produce a high volume at a low price as a low volume at a high price.

This implies that, at least as a first approximation, prices should be set per person immunized, not per dose. There is little reason to pay more per person immunized if more doses are required to provide immunity than if a single dose is required. In fact, the vaccine is more valuable if only a single dose is required to provide immunity, as this reduces delivery costs and is likely to increase patient compliance.

Moreover, the vaccine purchase program would not save money by excluding large countries from coverage, or excluding countries if vaccination is cost-effective at the marginal cost of production, but not at the average price paid for vaccine under the program. This is a false economy, because potential vaccine developers will need a fixed amount of revenue to induce them to conduct research, and if fewer doses are purchased, the price per person immunized will need to be greater to induce the same amount of research.<sup>21</sup>

Given the quantity of vaccines likely to be needed, the price per immunized person should be set so as to yield the desired market size. Market size should be large enough to stimulate research if scientifically warranted, but not so large that a vaccine would not be cost effective.

## 5.2 What Size Market Is Needed to Spur Research?

There is no single answer to the question of how large a market is needed to spur research. The larger the market for a vaccine, the more firms will enter the field, the more research leads each firm will pursue, and the faster a vaccine will be developed. The more researchers entering the field, the smaller the chance that any particular firm will be the first to

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<sup>21</sup> Excluding countries that would have bought vaccine in the absence of a program at prices greater than or equal to the price paid by the program would, however, increase incentives to develop vaccines. A sliding scale of co-

develop a vaccine. Thus the cost of development, adjusted by the risk that a particular firm or research team will not win the development race, rises with the potential size of the market.

Given the enormous burden of malaria, tuberculosis, and HIV/AIDS, it is important to provide sufficient incentive for many researchers to enter the field and to induce major pharmaceutical firms to pursue several potential leads simultaneously so that vaccines can be developed quickly.

Because potential vaccine developers know that their research may fail, in order to have incentives to conduct this work, they must expect to more than cover their research expenses if they succeed. For example, if potential biotechnology investors expect that a candidate vaccine has a 1 in 10 chance of succeeding, they would require at least a tenfold return on their investment in the case of success to make the investment worthwhile.<sup>22</sup>

There are several ways to get a sense of the minimum market size needed to motivate investors. DiMasi et al [1991], who examined 93 randomly selected new chemical entities from a survey of twelve pharmaceutical firms and found that, taking into account the risk of failure at each stage in the drug development process, the average cost per approved New Chemical Entity (NCE) was \$114 million 1987 dollars. Capitalizing this to the date of marketing approval at a (probably over-generous) 8 percent discount rate implies an average cost of \$214 million 1987 dollars, or approximately \$313 million 1999 dollars. While this figure is of some interest, there is wide variation in the cost of developing pharmaceuticals. DiMasi found that for most stages in the vaccine development process, the standard deviation of cost was greater than the mean cost.

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payments could be used to gradually phase out the program.

<sup>22</sup> As discussed in the companion paper, advocates for grant-funded research programs may have incentives to be over-optimistic about the prospects for easily developing vaccines. The Institute of Medicine estimated in 1986 that a malaria vaccine could be developed for \$35 million. This estimate is far too low. From the limited description of their methodology, it seems that their cost estimate assumes success in every stage of the vaccine development process, while in fact, it is likely that many different candidate vaccines will have to be tried before a usable vaccine is developed. A further indication that the Institute of Medicine's estimates were over-optimistic lies in their 1986 prediction that a malaria vaccine could be licensed within 5 to 10 years.

Vaccine trials for diseases with low incidence, such as HIV and tuberculosis, require very large samples, and are therefore expensive.<sup>23</sup>

The cost of developing malaria, tuberculosis, or HIV vaccines may be much higher than suggested by these estimates, since surveys of existing drugs and vaccines are disproportionately likely to focus on the low-hanging fruit of entities that are cheap to develop. Unfortunately, vaccines for malaria, tuberculosis, and HIV may not be such low-hanging fruit.

It is also useful to consider the revenue streams which seem sufficient to induce vaccine research in developed countries. The new Varivax vaccine against chickenpox is expected to average about \$177 million in annual revenue for the first 7 years of its sales [Merck Annual Report, 1998].

One approach to estimating the necessary size of a program is to ask pharmaceutical executives whether a vaccine purchase program could serve as an important incentive for research, and how big the program would need to be to do so. There are several reasons why this approach may give misleading results. First, the question is mis-specified. As discussed above, firms must decide not merely whether to invest in developing a particular vaccine, but also at what level to invest. The more lucrative a market, the more leads they will pursue. Second, pharmaceutical executives may see the question as part of a price negotiation, and may therefore inflate their estimates, particularly if they expect that budgets are likely to be cut in a process of negotiation. Third, pharmaceutical firms may well request programs that increase their profits, without necessarily increasing their incentives to develop a new vaccine. In particular, pharmaceutical executives may claim that the most useful motivator for HIV vaccine research would be higher prices on existing vaccines. Pharmaceutical executives clearly have an

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<sup>23</sup> Regulators may require large samples even for vaccines for diseases with higher incidence, because they believe it is especially important to detect potential side effects of vaccines, since they are administered to healthy people.

incentive to claim this, whether or not it is the case. Fourth, pharmaceutical firms have been criticized for failing to invest in research on vaccines for diseases which kill millions of people, while investing in more commercially viable drugs [Silverstein, 1999]. This may make executives reluctant to admit that they are not investing in vaccines because they think such vaccines would not be profitable. It is more politically acceptable for executives to say that they are not investing because they see few scientific prospects for such a vaccine. Finally, the key decision makers are not just pharmaceutical firms, but also biotech firms and their potential investors. Scientists working on vaccines may not have even considered the possibility of starting biotech firms or seeking investors, but if a large market were expected for vaccines, they might start thinking about this. Given that they probably have not spent that much time thinking about these issues yet, their responses to questions may not be that informative.

The opinion of outsiders, familiar with the industry, but not part of it, may be somewhat more credible. A respected pharmaceutical consulting firm estimates that a \$250 million annual market is needed to motivate pharmaceutical firms [Whitehead, 1999]. A ten-year purchase commitment would likely be sufficient to motivate research, given that potential vaccine developers are likely to heavily discount sales after this period, and that competing vaccines are likely to emerge after ten years in any case, and drive down prices to the point at which they could be more broadly affordable.<sup>24</sup> A condition of participation in the program could be agreement to license the vaccines to producers in developing countries after ten years of purchases at an appropriate level.

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<sup>24</sup> The life of a patent is 20 years. However, a vaccine would only reach the market several years after the date of application for a patent. The effective life of a patent is the number of years of remaining on the patent from the time that it is first brought to market. Shulman, DiMasi, and Kaitin [1999] report that the average effective patent life for new drugs and biologicals is 11.2 years under the Waxman-Hatch Act, which granted extra protection to inventors to partially make up for loss of patent life during regulatory review. Without the Act, patent life would be 8.2 years. The Act covers the U.S. only, and there is no reason to believe that developing countries will offer similar patent protection. As noted above, a requirement to license vaccines after ten years could potentially be built into

If politicians are unwilling to assume liability for more than a fixed amount of potential expenditure, coverage under the program could be capped. For example, suppose that a \$250 million annual market was deemed necessary to spur serious research on each vaccine, but that political leaders were unwilling to commit to more than \$520 million in potential annual expenditures on new vaccines. Suppose also that the chance that malaria, HIV, and tuberculosis vaccines were all developed simultaneously were judged to be less than 10 percent. Instead of only covering vaccines for two diseases, an alternative approach would be to pledge \$260 million in annual purchases for vaccines for any of the diseases, subject to a \$520 million cap on total committed annual expenditures. In the unlikely case that vaccines for three diseases were developed simultaneously, purchases for each would average one-third of \$520 million, or \$173 million. The expected market for a vaccine developer would be  $0.9 * \$260 \text{ million} + 0.1 * \$173 \text{ million}$ , or \$251.3 million.

### 5.3 Cost-Effectiveness

While the need to motivate research sets a lower bound on the size of the purchase commitment, the need for the program to be cost-effective when compared to alternative health interventions sets an upper bound on the size of a purchase commitment. This section argues that given the level of funding which is likely to be forthcoming, this is unlikely to prove a serious constraint. The World Bank calls health interventions that cost less than \$100/DALY saved highly cost effective [World Bank, 1993]. A program to purchase vaccines for malaria, tuberculosis, and HIV would be one of the most cost-effective health interventions in the world.

Appendix 2 contains preliminary estimates of the cost-effectiveness of commitments to purchase vaccines at various funding levels, vaccine efficacy levels, and required numbers of doses.

The base case we examine is based on an 80 percent effective one-dose vaccine and an average annual market of \$336 million for each vaccine. Donors would contribute approximately \$250 million annually, co-payments providing the remainder. The net present value of expenditures per discounted DALY saved over a ten-year horizon would be \$18 for malaria, \$33 for tuberculosis, and \$10 for AIDS. However, the benefits of the program will continue beyond the 10-year life of the purchase commitment as competing vaccines appear and prices fall. With competition the price of the vaccine is likely to fall to a level which is affordable for governments and agencies such as UNICEF. The NPV of expenditures per discounted DALY saved over an infinite horizon would be \$9 for malaria, \$21 for tuberculosis, and \$5 for AIDS. Overall, the cost would be about \$10/DALY. The cost-effectiveness may be underestimated, as these calculations do not take into account the likely reduction in secondary infections due to vaccinations. The vaccine price per person immunized in the first 10 years would be \$5.38 for malaria, \$2.03 for tuberculosis, and \$3.43 for HIV.

As discussed in Appendix 2, purchase commitments would remain cost-effective under a range of alternate assumptions about vaccine efficacy, the number of vaccine doses required, and the size of the fund.

#### **5.4 Increasing the Promised Vaccine Price over Time**

The sponsor of a vaccine purchase commitment program could start with a relatively modest program. If additional incentives were judged necessary to spur vaccine research, the

promised price could be increased until a vaccine were developed or the price reached the social value of a vaccine.<sup>25</sup> This procedure mimics auctions, which are typically efficient procurement mechanisms in situations in which production costs are unknown.<sup>26</sup>

As long as the price promised for a vaccine does not increase at a rate greater than the interest rate, firms will not have an incentive to sit on a vaccine they have developed while waiting for the price to rise. To see this, note that a firm which delays selling a vaccine postpones its returns into the future, and therefore has to discount these returns at the interest rate. In addition, delay risks the possibility that a competitor will introduce an alternative vaccine. Finally, if the vaccine developer has already taken out a patent, delay uses up the patent life.

If the price promised to vaccine developers was increased, this increase could potentially be restricted to vaccines which were based on patents that had not yet been taken out. Greater incentives may not be needed to stimulate the final stages of research on a candidate vaccine that is already promising. Moreover, restricting price increases to vaccines based on new patents reduces the chance that firms will withhold a product from the market in the hope that prices will increase. Pharmaceutical firms are not likely to risk delaying patent applications for fear that a competitor will preempt them, especially since there are potentially many competing biotech firms that could patent vaccines, whereas only a few large pharmaceutical firms actually conduct clinical trials and manufacture vaccines.<sup>27</sup> As discussed in Appendix 1, increasing the price over

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<sup>25</sup> Since the quantity purchased would stay constant, total revenue would rise in proportion to price.

<sup>26</sup> Another option would be to pre-announce that if no vaccine had been developed by a certain date, the price would start growing automatically. However, it is probably better to let future decision makers choose whether or not to increase the price, since in some scenarios it would be optimal not to increase the price. For example, there would be no need to increase the price if general technological advances in biology reduced the expected cost of developing a vaccine sufficiently that many firms decided to pursue vaccines.

<sup>27</sup> One potential problem with this approach is that vaccine developers might incorporate unnecessary late-patented components in the vaccine to qualify for a higher price. However, a committee could rule on what were the key patents used in a given vaccine, so simply adding an extra useless patent would not lead to a higher vaccine price.



time may induce firms to delay starting research on a vaccine, or slow down the pace of this research, but this strategic delay will not be severe if many firms can potentially compete to develop a vaccine. Moreover, while vaccine trials could not be conducted secretly, research towards patents could be, and this would make it much more difficult for potential vaccine developers to collude to increase the price by delay.

Appendix 1 uses techniques from the economic theory of auctions to examine the effect of increases in price on vaccine development. The main results are as follows: If there are many competing firms, a system in which the price starts low and rises over time will generate a vaccine at close to the lowest possible cost. The fewer competing researchers, the longer each waits before beginning vaccine research. The greater the initial price, the more rapidly a vaccine will be developed. This implies that if society values a vaccine highly, it should choose a high initial price, and thus be willing to incur the risk of paying more than the minimum cost necessary to spur vaccine development. In the most realistic case, increasing the growth rate of the price will speed vaccine development unless very few firms could potentially compete to develop the vaccine.

## **6. The Scope of a Purchase Commitment**

Potentially, advance purchase commitments could be used to encourage research not only on vaccines, but also on other techniques for fighting disease, including drugs, diagnostic devices, and insecticides against the mosquitoes which transmit malaria.

Covering a range of technologies would avoid biasing research effort towards vaccines, rather than other technologies to fight disease. The example of the British government's prize for a method of determining longitude suggests that prize terms should be set so as to admit a

variety of solutions. Most of the scientific community believed that longitude could best be determined through astronomical observations, whereas the actual solution was through development of a sufficiently accurate clock. Pre-specifying an astronomical solution would have been a mistake.

On the other hand, opening up the program to any method of fighting disease would make defining eligibility and pricing decisions almost impossible. For example, developers of new HIV counseling techniques could seek to obtain payments for new techniques for promoting safe sex. Resources would be wasted in disputes over the impact of such programs. If only vaccines for malaria, tuberculosis, and HIV were eligible, the resources wasted on administration and on attempts to influence the committee would likely be fairly small relative to the cost of developing a vaccine, since only those who had actually developed a vaccine would have an entry ticket to begin trying to influence the disposition of program funds. One factor that militates toward restricting the program to vaccines and drugs is that existing institutions, such as the U.S. FDA, already have a reputation for adjudicating safety and efficacy of vaccines and drugs. A safe, environmentally appropriate insecticide might be an excellent way to fight malaria, but a whole set of procedures would need to be developed to determine eligibility standards for insecticides. This suggests that research on insecticide might be better supported through push programs.

In principle, purchase commitments are appropriate for both drugs and vaccines, but if a choice has to be made for budgetary reasons, vaccines are probably a slightly higher priority, since distortions in vaccine markets are more severe. Since drugs are much more susceptible than vaccines to the spread of resistance, individual decisions to take drugs may potentially create negative, as well as positive, externalities. Moreover, drugs are widely considered to be

more profitable than vaccines, perhaps because consumers are reluctant to spend on vaccines for either behavioral or learning reasons.

Table 1 shows the number of deaths caused annually by various diseases for which vaccines are needed. Given a sufficient budget, it might be appropriate to commit in advance to purchase vaccines developed against any of these diseases. However, if funding is tightly limited, it may be appropriate to target the most deadly diseases.

**Table 1: Deaths from Diseases for which Vaccines Are Needed**

Diseases	Deaths (000) <sup>a</sup>	%
AIDS	2285	27.47
Tuberculosis	1498	18.01
Malaria	1110	13.34
Pneumococcus <sup>b</sup>	1100	13.22
Rotavirus	800	9.62
<i>Shigella</i>	600	7.21
<i>Enterotoxigenic E. coli</i>	500	6.01
Respiratory syncytial virus <sup>c</sup>	160	1.92
Schistosomiasis <sup>d</sup>	150	1.80
Leishmaniasis	42	0.50
Trypanosomiasis	40	0.48
Chagas disease	17	0.20
Dengue	15	0.18
Leprosy	2	0.02
Total deaths	8319	100.00

<sup>a</sup> Estimated, World Health Report, WHO, 1999

<sup>b</sup> A pneumococcus vaccine was just approved for use in the United States, but it needs to be tested in developing countries, and perhaps modified accordingly.

<sup>c</sup> The Jordan Report, NIAID, 1998

<sup>d</sup> R. Bergquist, WHO, personal communication

Source: Children's Vaccine Initiative, CVI Forum 18, July 1999, p. 6.

An alternative option would be to start with some easier-to-develop vaccines and drugs as a way of building credibility. It also may be useful to first experiment with purchase commitments for a few vaccines or drugs and then consider modifying or extending the program based on the resulting experience.

## **Conclusion**

For a vaccine purchase commitment to stimulate research investment, it must provide a credible promise that developers of good vaccines will be rewarded. Eligibility requirements could include both minimal technical standards, and the market test that developing countries be willing to provide a co-payment for the vaccine. To provide incentives for development of high-quality vaccines, bonus payments for vaccines could be tied, directly or indirectly, to the number of lives or DALYs saved by the vaccine, and to the delivery cost. The developer of the first viable vaccine could have market exclusivity unless subsequent vaccines are clinically superior. The vaccine price promised per immunized child could initially be set at a modest level, and could then be raised if it proved insufficient to spur enough research.

This conclusion briefly discusses the politics surrounding vaccine purchase programs. It then discusses the proposed U.S. tax credit for qualifying vaccine sales and the proposed World Bank \$1 billion fund for purchasing vaccines for future diseases. Finally, it discusses how a private foundation could implement a vaccine purchase commitment.

## **The Politics of Creating Markets for Vaccines**

Those with a stake in current aid programs and in grant-funded research programs may object to pull programs designed to create markets for vaccines, if they fear that resources would be drawn from important existing initiatives. Organizations involved in efforts to encourage condom use, for example, may fear that funds to develop an AIDS vaccine would be drawn from

prevention efforts. Academic and government scientists working on HIV research may be concerned that a vaccine purchase program may result in cuts in other important research programs. These groups are well placed to affect the political decision-making process.

Conflict between the need for incentives to develop new vaccines and existing prevention and research efforts will be limited if a purchase commitment is financed from pledges rather than current budgets. When a vaccine became available, it might be seen as justifying increasing the total aid budget. Alternatively, once a vaccine became available, some existing prevention efforts may be less cost-effective, and budget savings will be possible. The prospect of these future cuts will be politically easier than cutting existing programs, as future aid budgets do not have as much constituency among aid workers as current aid budgets. The people currently promoting condom use or researching HIV may have retired or gone on to other jobs by the time an HIV vaccine has been developed. It is worth noting that the budgetary conflict between research on new vaccines and efforts to control disease using existing technologies is sharper if research is financed out of current budgets, as it would be in push programs, than if it is financed through future vaccine purchases, which would come out of future budgets.

At least in the U.S. Congress, pharmaceutical firms are also likely to be a key player in discussions of how to encourage vaccine research and development. Pharmaceutical firms will be interested in seeing some expenditure early in the program. This may be in part because such expenditures would enhance the credibility of the commitment, and in part because a program rewarding, say, a malaria vaccine, would not necessarily yield high expected profits, since much of the profit would be dissipated in competition to develop the vaccine. It may be easier to find champions for such programs in the pharmaceutical industry if some portion of the funds can be used to cover vaccines which are closer to development. In particular, several new

pneumococcus vaccines are expected to be developed soon. Additional work will be needed to test the suitability of these vaccines for developing countries, and perhaps to modify them to reflect the strains of pneumococcus prevalent there. As currently written, the U.S. administration's proposal would cover new pneumococcus vaccines, since the disease kills more than a million people each year. Note, however, that one vaccine for pneumococcus has been licensed recently, and that under the administration's proposal, this particular vaccine would not be eligible, since it was developed before the legislation was passed.

### **Potential Sponsors of New Markets for Vaccines**

Commitments to purchase vaccines could be undertaken by governments of industrialized countries, the World Bank, or private foundations. One institution could establish the basic infrastructure for a program and make an initial pledge and other organizations could later make pledges of their own. The initial pledge could cover particular diseases or countries, with later pledges broadening the program. Nations might not want to pledge to a vaccine purchase commitment program operated under another donor nation's control, so it might make sense to build in procedures for representation of multiple donors on decision-making bodies at the start, even if the program were initially supported by only one or two donors.

The U.S. administration's budget proposal [<http://www.treas.gov/taxpolicy/library/grnbk00.pdf>] includes \$1 billion in tax credits on vaccine sales over the 2002-2010 period. The program would match every dollar of qualifying vaccine sales with a dollar of tax credit, effectively doubling the incentive to develop vaccines for neglected diseases. Qualifying vaccines would have to cover infectious diseases which kill at

least one million people each year, would have to be FDA approved, and would have to be certified by the Secretary of the Treasury after advice from the U.S. Agency for International Development. To qualify for the tax credit, sales would have to be made to approved purchasing institutions, such as UNICEF. Although the President's proposal is structured as a tax credit, it would have effects similar to an expenditure program that matched private funds spent on vaccines. The administration's proposal could help catalyze other funds for vaccine purchases, since it matches such purchases dollar for dollar.

The details of which vaccine sales would qualify would be worked out by the U.S. Agency for International Development (USAID) under the program, and the analysis in this paper suggests that the details of their procedures will be quite important for the effect of the program. Biotech and pharmaceutical firms are more likely to find the commitment credible if, once the tax credit legislation is passed, USAID quickly specifies guidelines for how it will allocate credits. In particular, USAID would need to specify how it will address issues of vaccine pricing (presumably, it would not approve credit allocations for a small quantity of vaccine sold at tens of thousands of dollars per person immunized), how much of the fund could be spent on a vaccine that is currently far along in research, such as the pneumococcus vaccine; and what procedures would be used to allocate credits if multiple versions of a vaccine were available.

The World Bank president, James Wolfensohn, recently said that the institution plans to create a \$1 billion loan fund to help countries purchase specified vaccines if and when they are developed [Financial Times, 2000]. Glennerster and Kremer [2000] discuss this proposal in more detail. Details of the Bank program have not been announced. One option under consideration is a more general program to combat communicable diseases of the poor. For a

general program to stimulate research, it must include an explicit commitment to help finance the purchase of new vaccines if and when they are developed. Without an explicit commitment along the lines proposed by Wolfensohn, it is unlikely that the large-scale investments needed to develop vaccines will be undertaken. As discussed in the companion paper, increased coverage of existing vaccines, while desirable in its own right, will by itself be inadequate to convince potential vaccine developers that there will be a market for new vaccines when they are developed, given the long lead times for vaccines and the fickleness of donor interest.

An explicit commitment to help finance purchases of new vaccines will not interfere with other initiatives to tackle communicable diseases of the poor. This is because the commitment does not have to be financed unless and until a vaccine is developed. So, for example, the Bank could increase lending to promote the use of bednets against malaria, or increase coverage of existing vaccines, while committing that if and when new vaccines are developed, it will provide loans to countries purchasing these vaccines.

Some within the Bank have traditionally regarded earmarking future credits for a particular purpose as undesirable because it reduces the flexibility of the Bank to provide loans where they would achieve the greatest benefit. Sacrificing flexibility is a mistake when it brings no compensating advantage. However, earmarking may be justifiable as a response to time-consistency problems. In particular, in the case of vaccines, earmarking can help resolve the time-consistency problem inherent in convincing potential vaccine developers that governments will compensate them adequately once they have sunk funds into developing vaccines. The loss of flexibility associated with earmarking does not seem like a major problem, since it would be hard to imagine a situation in which purchasing vaccines for malaria, tuberculosis, and AIDS would not be cost-effective. In any case, a commitment could be structured so that it would be



triggered only if a vaccine satisfied a particular cost-effectiveness threshold.

For countries to have an incentive to participate in the proposed World Bank program, loans will need to be at the concessional International Development Association (IDA) rates, and must not simply substitute for other concessional loans countries would have received. This is because commitments by one country to purchase vaccines benefit other countries by encouraging vaccine research and development. No one country, therefore, has a sufficient incentive to make a commitment on its own (the global public good problem.)

Private foundations could also play a major role in creating markets for new vaccines. Foundations may find it easier than governments to credibly commit to future vaccine purchases, given their greater continuity of leadership. In particular, the Gates Foundation has \$22 billion in assets, and one of its main priorities is children's health in developing countries, and vaccines in particular. U.S. law requires private foundations to spend at least 5 percent of their assets annually. This suggests that a way that "push" and "pull" incentives for vaccine development could be combined. A U.S. foundation could spend 5 percent of its assets annually on grants to help expand use of existing vaccines and provide for vaccine research. Meanwhile, the foundation could put its principal to use in encouraging vaccine research, simply by pledging that if a vaccine were actually developed, the foundation would purchase and distribute it in developing countries.

## Appendix 1: The Effect of Increasing the Promised Price for Vaccines

This appendix analyzes the effects of increasing the price pledged for a vaccine under the simplest model of auctions, in which each firm has a private cost of developing a vaccine, and these costs are independent. Suppose that the cost of developing a vaccine for pharmaceutical firm  $i$ , denoted  $c_i$ , is independently drawn from a distribution  $F$  with upper support  $\bar{p}$  and that there are  $N$  symmetrical pharmaceutical firms. Suppose the price  $p$  starts at some value  $\underline{p} < \bar{p}$  and then grows, or is expected on average to grow, at a constant rate until a vaccine is invented, or until  $p$  reaches  $\bar{p}$ .

An equilibrium consists of a function  $p_i(c_i)$  mapping each firm's cost into a price at which it will develop a vaccine. A necessary first-order condition for  $p_i(c_i)$  to be privately optimal is that the growth rate of surplus,  $p_i - c_i$ , must equal the discount rate plus the hazard rate that a rival firm will develop the vaccine. In the simplest case, in which bidders are symmetric and the cost of developing a vaccine is not correlated among bidders,  $p_i$  increases monotonically with  $c_i$ . Given monotonicity, the hazard rate that a rival will enter depends on the probability that a rival firm has a cost slightly greater than  $c_i$  conditional on no firm having a cost less than  $c_i$ . As the number of firms grows,  $p_i(c_i)$  declines, asymptotically approaching  $c_i$ , and the hazard rate that a rival enters grows without bound. Thus, if there were many symmetric pharmaceutical firms, this auction mechanism would lead a vaccine to be developed at a price very close to the cost of its development. Increasing the number of bidders not only reduces the expected price, but also reduces the expected time until a vaccine is developed given  $F$  and the growth rate of  $p$ .

At least over some range, increasing the growth rate of  $p$ , taking  $\underline{p}$  as fixed, will speed the time until a vaccine is developed. This is despite the fact that the first-order condition implies

that the faster the growth rate of  $p$ , or equivalently the lower the discount rate, the greater  $p_i(c_i)$ . To see why increasing the growth rate of  $p$  speeds the auction, note that if the growth rate of  $p$  is infinite, then the auction concludes immediately because the price immediately attains its upper limit of  $\bar{p}$ . As the growth rate of  $p$  approaches zero, the expected time for the auction to conclude grows without bound. Moreover, reducing the growth rate of  $p$  must asymptotically increase the time until a vaccine is developed, since as  $\dot{p}/p$  approaches zero,  $p_i(c_i)$  approaches its lower bound of  $c_i$ , and hence as the growth rate slows, the reduction in  $p_i$  is bounded, whereas the time it takes for the auction to reach any particular price increases without bound as the auction slows.

It seems likely that the expected time until a vaccine is produced typically declines with the growth rate of  $p$ , given  $\underline{p}$ , but if there are few firms, it is possible to construct examples in which the expected time until a vaccine is produced increases with the growth rate of  $p$ . If there are many firms, then  $p_i(c_i)$  will be very close to  $c_i$ , and hence reducing the growth rate of  $p$  will have little effect on  $p_i(c_i)$ , but will still lengthen the time required to reach any price. Hence, with many firms, a rapidly growing price, given  $\underline{p}$ , is likely to lead to a much faster vaccine discovery. On the other hand, if there are only a small number of firms, then  $p_i(c_i)$  may be significantly greater than  $c_i$ , and reducing  $p_i(c_i)$  may significantly shorten the auction. Consider the extreme case with only one firm. If  $p$  grows rapidly enough, the bidder will prefer to wait until the end of the auction, when the price reaches  $\bar{p}$ , before developing a vaccine. On the other hand, if the growth rate of the price is less than the interest rate, then once  $p/c_i$  is great enough, the vaccine will be developed. Thus, at least for some realizations of  $c_i$ , increases in the growth rate of  $p$  can lengthen the time until a vaccine is developed. If the distribution of the cost of development is such that most of the mass is at a low level, but there is a thin tail reaching up

to  $\bar{p}$ , then increases in the growth rate of  $p$  can lengthen the expected time until a vaccine is developed.

Holding constant  $\bar{p}$  and the growth rate of the price, the higher  $p$ , the shorter the time until a vaccine is developed. This suggests that the more a vaccine is valued, the greater  $p$  should be. In the extreme, if the social value of the vaccine is far greater than the upper support of  $c$ , then it would make sense to either have the price rise very quickly, or to choose  $p$  close to  $\bar{p}$ . Some may feel that the social value of vaccines is so great that it is better to spend more money than to risk delay, but this does not seem to be the revealed preference of rich country governments.

As long as the price does not grow that much faster than the interest rate, pharmaceutical firms will not actually sit on a vaccine they had already developed, waiting for the price to rise. Given discounting, it would be better for the firm to wait to begin research, rather than to first incur the cost of developing a vaccine, and then sit on the vaccine. Even if the firm got lucky and developed a vaccine faster than it expected, it would not sit on it if the growth rate of the program were equal to or less than the discount rate. Once a vaccine is developed, the opportunity cost of losing out to another bidder is not  $p - c_i$ , but rather  $p$ . The firm would only wait to develop the vaccine if the growth rate of  $p$  exceeded the discount rate plus the hazard rate that another firm would develop a vaccine.<sup>28</sup>

The optimal initial price depends on the expected cost of developing the vaccine, and therefore would generically differ between diseases. To see this, consider a hypothetical example in which each pharmaceutical firm faces its own cost of developing a vaccine, but it is common knowledge that the cost of developing a malaria vaccine is such that research would be

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<sup>28</sup> I am considering the case in which there is only one potential patented vaccine, so the winner reaps the entire

profitable at between \$5 and \$6 per person immunized, while the cost of developing an HIV vaccine is such that research would be profitable at between \$15 and \$16 per person immunized. Starting the auction at more than \$6 per person immunized would provide unnecessary rents to developers of a malaria vaccine. Starting the auction at less than \$15 per person immunized would unnecessarily delay the development of an HIV vaccine.

The analysis above treats the cost of developing a vaccine as independently distributed across bidders, but in practice, there are almost certainly common components to this cost, and to the benefits of selling a vaccine to the program. This will create some tendency towards a winner's curse. Firms might try to publicize any leads in research in order to deter rivals. This is a general feature of patent races, and is not specific to this mechanism. Since developing a vaccine involves many stages of research, and promising vaccines can fail at any stage from laboratory tests to animal trials to Phase 4 human trials, potential rivals are unlikely to believe that the leader has a lock on becoming the first to develop a vaccine.<sup>29</sup>

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reward.

<sup>29</sup> For example, rotavirus vaccine was recently withdrawn from the U.S. market, at least temporarily, following reports of side effects.

## Appendix 2: Preliminary and Rough Cost-Effectiveness Estimates

Rachel Glennerster<sup>30</sup> and Michael Kremer

This appendix reports some preliminary attempts at a rough estimate of the cost-effectiveness of a program to purchase vaccines for malaria, tuberculosis, and HIV. It considers a variety of funding levels for the program, efficacy levels for the vaccines, required number of doses, and coverage rates but focuses on a base case of a program providing an annual market averaging \$336 million per year for 10 years for purchases of each vaccine, of which donors would provide approximately \$250 million annually, and co-payments would cover the remainder. Our base case assumes that the vaccines will be 80 percent effective and require only a single dose to provide a lifetime of protection. Preliminary estimates suggest that the cost per Disability-Adjusted Life Year (DALY) saved, including the cost of co-payments, would be \$9 for malaria, \$21 for tuberculosis and \$5 for AIDS. (A DALY is a standard measure of the burden of disease which takes into account not only the years of life lost but the years of disability caused by a disease. The World Bank termed health interventions costing less than \$100 per DALY as highly cost effective [World Bank, 1993].) We then note that these estimates are likely to be conservative.

Below we discuss our assumptions about the DALYs saved by vaccines, manufacturing and delivery costs, coverage, and the share of costs covered through co-payments. We then present results on the number of doses delivered and program cost-effectiveness. Tables A1 and A2 summarize our assumptions and results. Table A3 shows sensitivity of the results to alternative assumptions of funding levels for the program, efficacy levels for the vaccines,

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<sup>30</sup> Rachel Glennerster wrote this while a visiting scholar at the Harvard Center for International Development. She is currently a staff member of the International Monetary Fund (IMF). The views expressed here are not necessarily

required number of doses, and coverage rates. Table A4 shows the cost per DALY saved in the base case relative to a counterfactual in which vaccines were not developed until fifteen years later. Further details of the calculations, including spreadsheets used in the analysis, are available from the authors. These spreadsheets can be used to examine the robustness of the analysis to alternative assumptions.

## **DALYs Saved**

The DALYs potentially saved as a result of the program are estimated using data on disease burden from the World Health Report [WHO, 1999]. This source estimates the DALY burden of various diseases in regions such as Africa and the Americas.<sup>31</sup> Geographic heterogeneity in burden of disease will lead us to underestimate the scope for targeting vaccine delivery, and thus the cost-effectiveness of a vaccine. (To see the logic in an extreme case, note that if a disease is spread evenly throughout a country, it is necessary to vaccinate everyone to protect the population, whereas if it is concentrated in one region, it may be possible to protect the population by immunizing only people in that area.) We have made very rough attempts to disaggregate the burden to individual countries within regions using data from World Health Organization [1998] for tuberculosis, UNAIDS [2000] for HIV/AIDS, and Gallup and Sachs

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those of the Executive Board or other members of the IMF staff.

<sup>31</sup> WHO provides information on the DALY burden of disease, which is calculated under the assumption that people would face a very favorable (Japanese) life expectancy in the absence of the disease. The DALY burden will, in general, be greater than the number of DALYs saved by eliminating the diseases, because the diseases affect countries where people face many other competing risks. This would bias estimated cost-effectiveness upward. To correct for this, we use the rough and ready approximation that the benefit of eliminating a disease in a country equals the burden of disease times the ratio of the present discounted value of a stream of benefits received over the expected lifespan in the country to the present discounted value of a stream of benefits received over the expected Japanese lifespan.

[2000] for malaria.<sup>32</sup> Within each country we allocate the burden to different age groups using the same proportions as in Murray and Lopez [1996]. We follow Murray and Lopez in applying a 3 percent real discount rate.

Our base case assumes that vaccines will have 80 percent efficacy. Most current vaccines have close to 100 percent efficacy, but newer vaccines may be less effective. We have not taken into account the DALYs saved from reductions in secondary infections. This effect is likely to be small for malaria, which has such a high reproductive rate in some parts of Africa that the chain of transmission is unlikely to be significantly disrupted by vaccination programs with realistic coverage rates. Studies have shown that even a dramatic reduction in the number of infected mosquitoes have little impact on the prevalence of the disease [Loutan et al]. For tuberculosis and HIV, many more secondary infections may be prevented, but the number is extremely difficult to estimate.

### **Manufacturing and Delivery Costs**

Manufacturing costs for most vaccines are quite low, although newer vaccines may well be more expensive to produce. Given that the package of five vaccines in the Expanded Program on Immunization (EPI) schedule sells for \$0.50 per dose, and that vaccines would be purchased

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<sup>32</sup> For tuberculosis and HIV/AIDS, these sources give number of infections by country, and we allocate the DALY burden in the same proportion. For malaria, Gallup and Sachs report only qualitative levels of prevalence. Percentages of the population living in low- and high-risk areas are reported for each country. Based on these probabilities and data on incidence of malaria in limited countries, we gave a weight of 1 to low-risk and 10 to high-risk areas and weighted according to the population living in low- and high-risk regions. For example, if 20 percent of the population live in low-risk areas, 50 percent live in high-risk areas, and 30 percent live in areas without malaria, the estimated proportion of burden for the country is  $(1 \times 0.2 \times 100) + (10 \times 0.5 \times 100)$ . The regional DALYs were then allocated to individual countries in proportion to these proportion of burden numbers. Although the calculation is very rough, it affects only the distribution of burden among countries, not overall burden.



in bulk under the program, it seems reasonable to assume that manufacturing costs would be \$0.50 per immunization.

Our base case is that of a vaccine requiring a single dose which could be added to the standard package of vaccines that are delivered under the EPI package. The package, which includes 3 contacts with each child, costs \$15, or \$5 for every contact [World Bank, 1993]. The majority of this cost is delivery cost as the price of the EPI vaccines is very low. We assume that the additional delivery cost of adding one additional vaccine to the package will not exceed \$1.00. This seems safe given that the World Bank estimated that adding two new vaccines to the EPI package would increase the cost of the package by 15 percent, or \$2.25, including both the purchase price and the delivery cost [World Bank, 1993]. Manufacturing and delivery costs are assumed to be constant in real terms over time. We assume that coverage of new cohorts of children will be the same as for the EPI package (i.e., that three-quarters of each new cohort of children will be immunized).

Delivering a vaccine to older children and adults will be more expensive since a delivery system is not already in place. It is likely to be relatively cheaper to vaccinate those who are already gathered in one place, such as school children and pregnant women attending pre-natal clinics. Reaching other groups is likely to be more expensive.

The delivery cost is also likely to rise with the percentage of the population which is targeted, as some people, such as those who live in cities and regularly use the health care system, will be easy to reach, while others, who live in remote areas and are unwilling to come to clinics, will be difficult to reach. We have assumed that 30 percent of the population aged 1-35 will be immunized against tuberculosis and AIDS in the first year. After the first year, only new cohorts will be immunized against these diseases. The delivery cost for reaching 30 percent of

children aged 1-10 is assumed to be \$3, while the delivery cost for reaching 30 percent of people aged 11-35 is assumed to be \$5, the average cost of a contact with the EPI program.<sup>33</sup> Note that actual delivery costs might be much lower, as 30 percent of adults may well seek vaccination on their own.

We assume a malaria vaccine would be targeted to children under 5 and to first-time mothers, the two groups for which the disease is most often fatal.<sup>34</sup> Clinics already exist which provide medical services to pregnant women in many developing countries. We therefore assume that 50 percent of women pregnant with their first child will be immunized against malaria each year for the first 20 years at a cost of \$3 per woman. After this, most first-time mothers will have already been immunized as children. We have assumed that  $\frac{1}{4}$  of births are to first-time mothers. We also assume that 50 percent of one to five year olds are vaccinated against malaria. For HIV/AIDS and tuberculosis, we assume that 30 percent of the stock of unimmunized 11 to 35 year olds, and 75 percent of children in new cohorts will be vaccinated.

### Co-Payments

We assume co-payments per immunized person of 0.25 percent of per capita Gross National Product (GNP) for HIV/AIDS, 0.06 percent of per capita GNP for tuberculosis, and 0.16 percent of per capita GNP for malaria. (These percentages are chosen to be proportional to the DALY benefits of each vaccine per person immunized, since willingness to pay presumably increases with DALY benefits per person vaccinated.) For concreteness, this implies that for a

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<sup>33</sup> Under our assumptions, it is cost effective to vaccinate newborns against HIV/AIDS rather than to wait until they become older, even though this means delivery costs must be incurred sooner, because it is much cheaper to immunize people as part of the EPI program.

<sup>34</sup> Young children have not yet developed limited natural immunity, and primiparous women have weakened

low-income country, such as Kenya, with GNP per capita of \$340, the co-payment would be \$0.83, \$0.19, and \$0.56 per immunization for HIV/AIDS, tuberculosis, and malaria, respectively.

## **Results**

### **Number of Vaccinations**

As discussed in section 5.1, once a vaccine has been developed, it should be used wherever it is cost effective given manufacturing and delivery costs. Using the assumptions above on the DALY burden of disease and costs of vaccine manufacturing and delivery, we calculate the marginal cost per DALY of vaccination for each of the three different age groups in each country. Vaccination is assumed to be cost effective if the marginal cost of delivery and manufacturing is less than \$100 for every DALY saved. For example, sixty-four countries have high enough malaria burden that immunization of new cohorts would be cost effective. Widespread immunization of new cohorts would be cost effective in 112 countries for tuberculosis, and in 75 countries for HIV.

Overall, we find that in the first 10 years of the program, it would be cost effective to vaccinate 625 million people against malaria, 1,656 million people against tuberculosis, and 980 million people against HIV (Table A2).

### **Purchase Cost, Co-Payments, and Cost-Effectiveness**

Given an average annual market of \$336 million for each disease, and the number of immunizations projected above, the price per immunization would be \$5.38 for malaria, \$2.03 for tuberculosis, and \$3.43 for AIDS. The total value of co-payments over 10 years would be \$0.6 billion for malaria, \$0.7 billion for tuberculosis, and \$1.3 billion for AIDS. As a larger number of people are assumed to be immunized in the first year than in subsequent years, the payment to the developer will be front loaded.

After the 10 years of the program we assume that competing vaccines will be developed, and prices will fall. With competition, we assume that the vaccines can be purchased by governments or UNICEF at a price equal to the manufacturing cost, which is assumed to be \$0.50 per immunization. For net present value calculations we use a nominal discount rate of 5 percent and a real discount rate of 3 percent.

The net present value (NPV) of purchase and delivery costs, over 10 years, would be \$3.5 billion for malaria, \$6.8 billion for tuberculosis and \$4.3 billion for HIV. The program would be highly cost effective even in the short run, with a NPV cost per discounted DALY saved over the first 10 years of \$18 for malaria, \$33 for tuberculosis, and \$10 for HIV. However, the benefits of the program will continue beyond 10 years. The NPV cost per discounted DALY saved over an infinite horizon would be \$9 for malaria, \$21 for tuberculosis, and \$5 for HIV. Overall, the cost per DALY saved would average \$10.

### **Sensitivity Analysis**

Estimating DALY burdens and assessing the marginal cost of vaccination involves many difficult judgments, and it would be a mistake to attach even a moderate degree of precision to

these estimates. Yet even if the calculations of the program cost per DALY saved were off by a factor of 5 for tuberculosis or a factor of 18 for HIV/AIDS, they would still meet the World Bank's cost-effectiveness criteria of \$100/DALY.

The program remains highly cost effective under a variety of sensitivity checks. Table A3 shows that the program would be highly cost effective even if vaccine efficacy were only 30 percent. (The tuberculosis vaccine does become considerably less cost effective, but still easily passes the \$100/DALY cost-effectiveness threshold.) Note that as the efficacy of a vaccine declines, the number of people for whom vaccinations are cost effective at a threshold of \$100/DALY declines.

Panel 2 of Table A3 shows that changing the cost-effectiveness threshold at which people are vaccinated has only a minor impact on the discounted cost of the program per DALY saved, and that the number of people vaccinated does not fall dramatically if the cost-effectiveness threshold is set at \$50/DALY rather than \$100/DALY.

Panel 3 shows that increasing the required number of doses significantly raises program costs, given our assumptions. This is because delivery costs are a large portion of overall program costs. However, even if a vaccine requires three doses, the program would remain highly cost effective.<sup>35</sup>

The fourth panel shows how the cost-effectiveness of the program varies with the size of the market promised to vaccine developers. Doubling the size of the market promised to vaccine developers increases the cost per DALY by considerably less than a factor of two. This is because delivery costs represent a large share of overall costs, and they are unaffected by increasing the price paid to vaccine developers.

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<sup>35</sup> Note, however, that we have not adjusted for the lower compliance rates to be expected when more doses are required. This awaits further work.

Panel 5 shows the effect of changing the discount rate used. Most cost-effectiveness analyses of health programs assume a 3 percent discount rate, and to maintain consistency with this literature, we also assume a 3 percent discount rate. However, the program would still be highly cost effective at a 5 percent discount rate.

The final panel shows scenarios with different vaccination rates. The first line shows the base case with 75% of new cohorts, 50% of pregnant women and school children, and 30% of other targeted existing cohorts vaccinated. The second line shows a vaccination rate of approximately 2/3 the base case, with 50% of new cohorts, 35% of school children and pregnant women, and 20% of other existing cohorts reached.

The base case analysis above implicitly assumes that vaccines would not be developed in the absence of a program. One can also consider the case in which vaccines would eventually be developed in the absence of a program, but they would take longer to be developed. Given the extremely small incentives for vaccine development now, the long lead times, great risk, and high expense involved in vaccine testing and licensing, it seems likely that in the absence of a concerted program, vaccines would not be available for a long time. We consider the case in which the introduction of a vaccine would be delayed by fifteen years in the absence of an incentive program. Note also that under current institutions, new vaccines may take ten or twenty years after they are introduced to achieve wide use in poor countries, because they are initially priced at high levels, and many developing countries cannot afford them. We will assume that in the absence of a program, countries with per capita incomes below \$500 could not afford vaccines for the first ten years after the vaccines were introduced.

The first row of Table A4 shows the cost per DALY saved of the program relative to a counterfactual in which a vaccine was developed fifteen years later which sold for \$2 per dose

and had the same country coverage as under the program. The second row shows the cost per DALY saved under the program relative to an alternative in which vaccines were developed fifteen years later, sold for \$2 per dose, and did not reach countries with incomes under \$500 per capita until an additional ten years had passed. The latter case seems more realistic, given experience with previous vaccines.

These estimates are likely to be conservative, as we have not taken into account some important but hard to quantify effects. 1) As noted above, immunization programs are likely to reduce secondary infections, particularly for HIV and tuberculosis. 2) We have assumed that the population and prevalence of the diseases are at steady state. Given the fixed costs of research and development, population growth will tend to reduce the price per immunization and the cost-effectiveness of the program. 3) HIV prevalence is growing rapidly, which would lower the cost of the program per DALY saved. 4) It is possible that with widespread immunization, the diseases would be eradicated, at least in some regions. In this case the benefits of the program would continue while the delivery and manufacturing costs would fall. 5) We have neglected benefits flowing to rich countries, which are important for HIV/AIDS and tuberculosis. 6) We have assumed reasonably high manufacturing and delivery costs. 7) We have not allowed for any targeting of vaccine delivery to areas of particularly high prevalence within countries, which would improve cost-effectiveness.

## Cost-Effectiveness

**Table A1. Base Case Assumptions**

Real discount rate	0.03
Inflation	0.02
Vaccine efficacy	80%
Groups targeted from existing cohorts: HIV/AIDS	1 to 35 year olds
Groups targeted from existing cohorts: malaria	1 to 5 year olds, first-time mothers
Groups targeted from existing cohorts: tuberculosis	1 to 35 year olds
Coverage for new cohorts	75%
Coverage for existing cohorts: HIV/AIDS and tuberculosis	30%
Coverage for existing cohorts: malaria	50%
Average annual purchase cost per disease (millions)	\$336
Manufacturing cost per person immunized	\$0.50
Delivery cost: new cohorts	\$1.00
Delivery cost: 1-10 year olds, pregnant women	\$3.00
Delivery cost: 11-35 year olds	\$5.00
Period for which vaccination is effective	lifetime
Worldwide HIV/AIDS DALY burden (millions)	70.9
Worldwide malaria DALY burden (millions)	39.3
Worldwide tuberculosis DALY burden (millions)	28.2

**Table A2. Base Case Results**

	HIV/AIDS	Malaria	Tuberculosis	Total
<b>Over a ten-year horizon</b>				
Vaccinations (millions)	981	625	1656	3262
Price to developer per vaccination	\$3.43	\$5.38	\$2.03	\$3.09
Average co-payment per vaccination	\$1.30	\$0.95	\$0.39	\$0.77
Donor contributions needed per year (millions)	\$209	\$277	\$271	\$757
Discounted DALYs saved (millions)	544	221	228	993
NPV cost per discounted DALY saved (including co-payments)	\$9.93	\$18.12	\$32.55	\$14.67
<b>Over an infinite horizon</b>				
NPV cost per discounted DALY saved	\$5.42	\$8.52	\$20.65	\$10.47



**Table A3: Sensitivity Analysis**

Entries in each cell are the cost per DALY saved over an infinite horizon, and in parentheses, the number of people vaccinated over the first ten years (in millions).

	<u>HIV/AIDS</u>	<u>Malaria</u>	<u>Tuberculosis</u>
<u>Vaccine efficacy</u>			
30%	\$13.36 (846)	\$20.60 (479)	\$49.08 (1301)
50%	\$8.30 (906)	\$13.34 (594)	\$30.63 (1446)
80%	\$5.42 (981)	\$8.52 (625)	\$20.65 (1656)
100%	\$4.34 (986)	\$7.85 (840)	\$16.70 (1684)
<u>Cost-effectiveness threshold for coverage</u>			
\$50 per DALY	\$5.17 (899)	\$8.27 (582)	\$18.77 (1364)
\$100 per DALY	\$5.42 (981)	\$8.52 (625)	\$20.65 (1656)
\$500 per DALY	\$6.51 (1326)	\$10.64 (996)	\$21.17 (1720)
<u>No. of doses required</u>			
1	\$5.42 (981)	\$8.52 (625)	\$20.65 (1656)
2	\$8.10 (899)	\$12.04 (571)	\$31.32 (1364)
3	\$9.13 (712)	\$13.97 (466)	\$37.29 (1275)
<u>Size of fund</u>			
\$250 million	\$4.85 (981)	\$7.35 (625)	\$19.08 (1656)
\$336 million	\$5.42 (981)	\$8.52 (625)	\$20.65 (1656)
\$500 million	\$6.50 (981)	\$10.80 (625)	\$23.60 (1656)
<u>Real interest rate</u>			
3%	\$5.42 (981)	\$8.52 (625)	\$20.65 (1656)
5%	\$8.85 (932)	\$11.29 (600)	\$34.55 (1381)
<u>Immunization rate</u>			
base case	\$5.42 (981)	\$8.52 (625)	\$20.65 (1656)
2/3 base	\$6.53 (654)	\$10.82 (425)	\$23.69 (1104)

**Table A4: Cost per DALY Saved Relative to Counterfactual in which Vaccines Were Developed Fifteen Years Later**

<u>Access to Vaccine in First Fifteen Years</u>	<u>HIV/AIDS</u>	<u>Malaria</u>	<u>Tuberculosis</u>
All countries	\$23.17	\$30.89	\$73.49
Countries with GNP > \$500 per capita	\$11.35	\$17.08	\$39.94

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